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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/666,311

Applicant(s)

DAHIYAT ET AL.

Examiner

Michael Borin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) ____ is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Status of Claims

1. Response to restriction requirement filed 10/04/04 is acknowledged. Applicant elected, without traverse, Group III, claims 4-8. Claims 1-3 are canceled. Claims 4-8 are pending.

Information Disclosure Statement

2. Applicants' Information Disclosure Statement filed 07/30/04 has been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 4-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.
 - A. Claim 4, step (b): It is not clear, whether generating probability table means calculating probability of appearance of a given residue in the given sequence (e.g., probability of finding alanine residue in a given sequence obtained in step a)) or

probability of appearance of various residues in a given position of a protein. The latter is assumed in this Office action.

In any event, the relation of step b) to subsequent method steps is not clear. It is not clear how the generating the table effects next method step.

B. Claim 4, step c): It is not clear which "said amino acid residues" are being combined. Preceding method step b) mentions an amino acid residue" only as a source for generating a probability table; hence, it is not clear whether the residues themselves are being combined (and how then the resulting sequence is different from the primary sequence – in the sequence of combined residues?), or combining residues which are "probable" to be in said residues according to the Table.

C. Claim 4, step d): It is not clear how process of "ranking" a library generates another library - it seems that the library has already been "generated" in step (c).

D. Claim 7 : the term "mutation" lacks antecedent basis – there was no mutation addressed in the preceding claims.

Claim Rejections - 35 U.S.C. § 101/ 112-1

4. Claims 4-8 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. The specification at page 5, lines 13-24 discloses that the present invention is directed to methods of using computational screening of protein sequence libraries to select smaller libraries of protein sequence that can be used in a number ways. For example, the proteins can be actually synthesized and experimentally

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tested in the desired assay, improved function and properties. Similarly, the library can be additionally computationally manipulated to create a new library which then itself can be experimentally tested. However, creating a library for further screening or testing is not a utility for the method. A library is similar to a composition in nature that has to undergo screening to isolate and identify a product. The court in *Brenner v. Manson*, 148 U.S.P.Q. at 689 expressed the opinion that chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in U.S.C. 101, which requires that an invention must have either an immediately apparent or fully disclosed "real world " utility. The court held that:

The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.. . a patent is not a hunting license. . . is not a reward for the search, but compensation for its successful conclusion. Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use or testing "

Brenner, 148 USPQ at 696.

The instantly claimed method provide for generating a secondary library of as yet undetermined structure, function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the secondary library was, as of the filing date, useful for any industrial or any pharmacological uses. Until some actual and specific significance can be attributed to the secondary library or even the compounds present the library, an artisan

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would be required to perform additional experimentation in order to determine how to use the generated secondary library. Thus, there was no immediate "real world " utility as of the filing date. Because any potential pharmacological utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in any specific and practical form. The specification does not disclose substantial interpretation for the result; and none is known in the art. In order for generated library to be useful, as asserted, for any pharmacological use, there must be a well- established or disclosed claimed library correlation or relationship between the and a disease or disorder. The secondary library of as yet undefined structure allegedly generated from the claimed method does not have a specific and substantial or real-world utility well-established utility.

5. Claims 4-8 are also rejected under U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 103.

6. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 4-8 are rejected under 35 U.S.C. 103 as being obvious over Srinivasan (US Patent 5,884,230) or Srinivasan et al. (Biomacromolecules: From 3-D to Applications, Hanford Symposium on Health and the Environment, 34th, Pasco, Wash., Oct. 23-26, 1995 (1997), Meeting Date 1995, 69-81. Editor(s): Ornstein, Rick L. Publisher: Battelle Press, Columbus, Ohio) in view of Altshul (Nucleic Acid Research, 1997, vol. 25,3389-3402) and Levitt (Biochemistry, 1978, 17, 4277-4284) and Lacroix et al (US 2002/0072864; filing date 08/31/1999) and further in view of Mayo et al (US 6,269,312).

The claims are drawn to method for generating a secondary library of protein variants comprising:

- a) generating library of sequences using an alignment program;
- b) generating a probability distribution table of variant amino acid residues in a plurality of positions;
- c) combining residues to generate secondary library;
- d) ranking the secondary library

e) synthesizing protein variants from secondary library.

Srinivastan et al describe method of protein modeling which generates sequence of a model protein using alignment program, identifies three-dimensional structure of the model protein, geometrical constraints required to maintain the structure, and then populates the three-dimensional space with amino, which are either original residues of the model protein or their equivalents (see cols. 4-5). The method uses position identity matrix for various residues at a given position (col. 10). Similarly, same authors describe homology guided protein design in "Biomacromolecules, 1997, wherein the replacing residues were selected from either those known to be conserved in the family of proteins (p. 76, bottom) – i.e., having high probability to be in a given location – or, by similar mimetics (p. 77). Although the references do not specifically suggest using table of "probability distribution of variant amino acid residues" use of such approach would be obvious to generate and test protein models made of homologous sequences, because it is known that for any given protein position certain residues are most probable than other, and such residues can be selected from probability distribution tables. See, for example, Altshul et al describing use of probability distribution of residues in aligning proteins or Levitt et al teaching conformational preferences of amino acids in proteins. See Altshul, abstract, and pages 3394, last full paragraph through p. 3395. or Laxroix et al using probabilities of having particular residue in calculating possible rotamers in protein structure. See Levitt, abstract, and p.4284, last paragraph. See Laxroix et al., paragraph [0164]. Therefore, it would be obvious for an artisan to be motivated, in the process of creating a model protein, to select such residues that are likely to occur at the given protein position, or in other

words to select such residues that will be feasible judged by probability of their presence in a given position.

Srinivastan does not use the term "libraries" in regard to initial and final protein structures obtained in the course of protein modeling. However, it would be obvious to an artisan that iterative process of alignment and modeling will produce plurality of both starting and modeled therefrom structures which read on the "primary" and "secondary" sequences (or libraries) of instant invention.

In regard to the "ranking" step of the instant method, the relevance of the this step in "generating" secondary library (which had already been generated) is not clear; therefore Examiner does not see patentable weight in this limitation. In any event, use of various types of ranking and scoring of modeled protein structures is well known in protein modeling. See, for example, Mayo et al (US 6,269,312), columns 17-25.

Finally, in regard to synthesizing step, it would be obvious to one skilled in the art that the desirable end stage of any protein modeling is synthesis of proteins of interest. Further, selection of PCR method to synthesize proteins would be obvious to an artisan as it is one of the main methods of protein synthesis, and selection of particular parameters of PCR would be obvious to an artisan as a part of routine selection of optimal parameters.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 4-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-8 of U.S. Patent No. 6,403,312¹.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '312 claims teach method for generating

¹ As assignee information was not available at the time of preparing Office action, Examiner assumes that the instant application and the reference has common assignee.

secondary library comprising steps of providing a first library, generating a probability distribution of amino acid residues in a plurality of variant positions, and synthesizing a plurality of modeled proteins. Although the claims of '312 are not specifically drawn to using alignment program in generating primary library, this will be an alternative approach obvious to an artisan; in addition, the specification, col. 8, lines 9-15, clearly identifies use of alignment software.

9. Claims 12, 21-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-29 of copending Application No. 09/927790.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claims in 09/927790 claims teach method for generating secondary library comprising steps of generating primary protein library, generating a probability distribution table of variant amino acid residues in a plurality of positions; combining residues to generate secondary library; ranking the secondary library, and synthesizing protein variants from secondary library. Although the claims of 09/927790 are not specifically drawn to using alignment program in generating primary library, this will be an alternative approach obvious to an artisan.

This is a provisional obviousness-type double patenting rejection.

Conclusion

10. No claims are allowed

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11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD, can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Borin, Ph.D.



Primary Examiner

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